



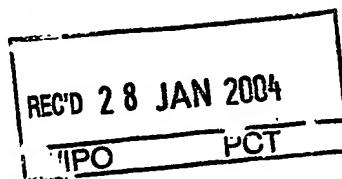
10/538028
4-S-3371
PCT/EP 03/14082



INVESTOR IN PEOPLE

PRIORITY DOCUMENT

SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH RULE 17.1(a) OR (b)



The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

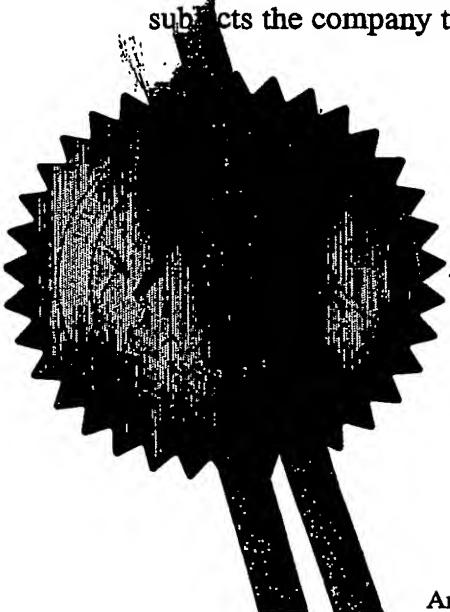
I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 17 October 2003

BEST AVAILABLE COPY

16 DEC 2002

1 / 77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form.)

16 DEC 2002

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1. Your reference	4-32799P1		
2. Patent application number <i>(The Patent Office will fill in this part)</i>	0229280.3		
3. Full name, address and postcode of the or of each applicant <i>(underline all surnames)</i>	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND <i>7125487005</i>		
Patent ADP number <i>(if you know it)</i>			
If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND		
4. Title of invention	Organic compounds		
5. Name of your agent <i>(If you have one)</i>	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH		
Patents ADP number <i>(if you know it)</i>	1800001		
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and <i>(if you know it)</i> the or each application number	Country	Priority application number <i>(if you know it)</i>	Date of filing <i>(day/month/year)</i>
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? <i>(Answer 'Yes' if:</i>	Date of filing <i>(day/month/year)</i>		
a) <i>any applicant named in part 3 is not an inventor, or</i>	Yes		
b) <i>there is an inventor who is not named as an applicant, or</i>			
c) <i>any named applicant is a corporate body.</i>			
<i>(see note (d))</i>	BEST AVAILABLE COPY		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description	10 ✓
Claim(s)	5 ✓
Abstract	
Drawing(s)	

Cf

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (<i>Patents Form 7/77</i>)	
Request for preliminary examination and search (<i>Patents Form 9/77</i>)	One
Request for substantive examination (<i>Patents Form 10/77</i>)	
Any other documents (please specify)	

11.

I/We request the grant of a patent on the basis of this application

Signature

Date

B. A. Yorke & Co.

B.A. Yorke & Co.

16 December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. J. Crook
020 8560 5847

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

- If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.
- Write your answers in capital letters using black ink or you may type them.
- If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.
- Once you have filled in the form you must remember to sign and date it.
- For details of the fee and ways to pay please contact the Patent Office.

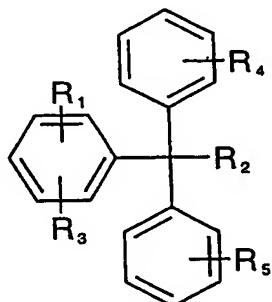
DUPLICATE

Organic Compounds

The present invention relates to a process for preparing organic compounds and to intermediate compounds in such a process.

More particularly, the invention relates to:

(A) a process for preparing a compound of formula I or a salt thereof

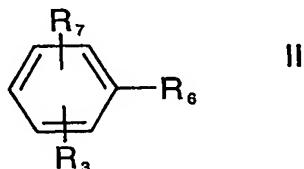


wherein R₁ is a reactive substituent or an attachment to a solid phase;

R₂ is a reactive substituent; and

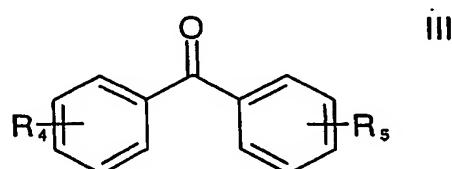
R₃, R₄ and R₅ are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, C₁₋₁₀-alkylamino, di-C₁₋₁₀-alkylamino, carbamoyl, C₁₋₁₀-alkylcarbamoyl, di-C₁₋₁₀-alkylcarbamoyl, halo-C₁₋₁₀-alkyl, halogeno or nitro; comprising

(a) (i) reacting a compound of formula II with a metal or organometallic compound



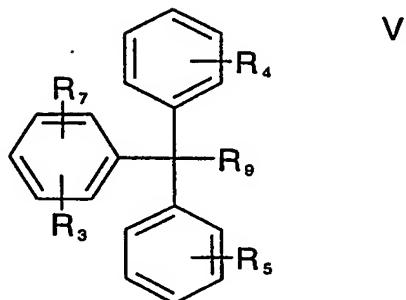
wherein R₆ and R₇ are each a nucleophilic substituent and R₃ is as defined above and is protected if necessary by a removable protecting group; and

(ii) reacting the compound obtained in (i) with a compound of formula III



wherein R₄ and R₅ are as defined above and are protected if necessary by a removable protecting group;

to form a compound of formula V



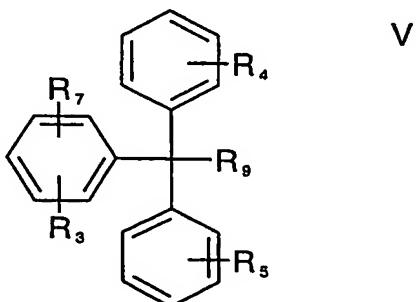
wherein R₃, R₄, R₅ and R₇ are as defined above;

R₉ is -OH, -OM or -OMX, where M is metal and X is a nucleophilic substituent; and

- (b) (i) reacting the compound of formula V with a metal or organometallic compound, and
 - (ii) reacting the compound obtained in (b) (i) with an electrophile, and hydrolysing the resulting compound to form a compound of formula I wherein R₂ is hydroxy;
- (c) optionally converting the hydroxy as R₂ to an alternative R₂ group;
- (d) optionally converting R₁ to an alternative R₁ group;
- (e) optionally deprotecting a compound of formula I in protected form; and
- (e) where required, converting a compound of formula I obtained in free form into the desired salt form, or vice versa;

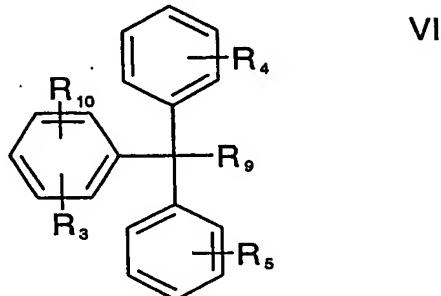
(B) a process for the preparation of a solid phase support system, comprising preparing a compound of formula I by a process as defined above, and coupling the compound with a suitably derivatised or functionalised solid phase material;

(C) a compound of formula V in free or salt form



wherein R₃, R₄, R₅, R₇ and R₉ are as defined above;

(D) a compound of formula VI in free or salt form



wherein R_3 , R_4 , R_5 and R_9 are as defined above; and
 R_{10} is $-M$ or $-MX$, where M is metal and X is a nucleophilic substituent.

The present invention provides a simple route for the preparation of compounds of formula I, which are useful for solid phase chemical synthesis. The process of the invention may directly produce a compound of formula I attached to a solid phase, or where R_1 is a reactive substituent, the compound of formula I can easily be coupled to a solid phase at a later stage. The presence of the reactive substituent R_2 permits the use of the compounds of formula I as linkers in the synthesis of oligomers and polymers, such as glycopeptides, nucleotides and proteins, especially in the solid phase synthesis of peptides. The compounds of formula I, particularly where R_2 is halogeno, may also be used as protecting agents for protecting functional groups, e.g. amino or hydroxy groups, in chemical synthesis.

The compounds of formula V and VI are useful as intermediate compounds in the preparation of compounds of formula I.

The process of the present invention, for example process steps (a) and (b), may suitably be performed in a single reaction vessel without intermediary isolation.

Terms used in the specification have the following meanings:

"Alkyl" may be straight or branched. Preferably alkyl is C_{1-4} -alkyl.

"Alkoxy" may be straight or branched alkoxy. Preferably alkoxy is C_{1-4} -alkoxy.

"Acylamino" denotes a group of formula $-\text{NH}-\text{C}(\text{O})-\text{R}$ where R is straight chain or branched C₁₋₁₀-alkyl, cycloalkyl or aryl, for example phenyl. Preferably R is C₁₋₄-alkyl.

"Acyloxy" denotes a group of formula $-\text{O}-\text{C}(\text{O})-\text{R}$ where R is straight chain or branched C₁₋₁₀-alkyl, cycloalkyl or aryl, for example phenyl. Preferably R is C₁₋₄-alkyl.

"Aryl" is preferably C₆₋₁₀ aryl.

"Halogeno" means fluoro, chloro, bromo or iodo.

"Haloalkyl" means straight chain or branched C₁₋₁₀-alkyl, substituted by one or more, for example one, two or three halogen atoms, preferably fluorine or chlorine atoms. Preferably haloalkyl is C₁₋₄-alkyl substituted by one, two or three fluorine or chlorine atoms.

"Organometallic compound" denotes a compound in which a carbon atom of an organic group is bound to a metal. The organometallic compound is preferably an alkylmetallic compound, for example an alkyl lithium, e.g. a straight or branched chain C₁₋₁₀ alkyl lithium compound or may alternatively be an arylmetallic compound, for example an aryl lithium. More preferably the alkyl lithium compound is a C₃₋₅ alkyl lithium compound, such as butyllithium.

Alternatively, the organometallic compound may be an organomagnesium compound, for example a straight or branched chain alkylmagnesium or arylmagnesium compound, preferably a C₁₋₆ alkylmagnesium compound. Organomagnesium compounds are commonly known as Grignard reagents. The organomagnesium compound is preferably an organomagnesium halide, especially an iodide or bromide.

In further alternative embodiments, the organometallic compound may be an alkyl- or arylzinc compound, for example a C₁₋₆-alkylzinc compound, or an C₁₋₆-alkyl- or aryltin compound.

Where a metal is used, the metal is preferably lithium or magnesium.

R₁ may be a reactive substituent suitable for linking the compound to a solid phase. R₁ may suitably be -C(O)R', -C(O)-OR', -C(O)-NR'R'', -R₁₂-NR'R'', -R₁₂-OR', -NR'R'', or -C(O)X, wherein R' and R'' are each independently hydrogen or straight or branched C₁₋₁₀-alkyl, e.g. C₁₋₄-alkyl, R₁₂ is straight or branched C₁₋₁₀-alkyl, e.g. C₁₋₄-alkyl, and X is a nucleophilic substituent, preferably halogeno, e.g. chloro. R₁ may suitably be in the para, ortho or meta position, preferably in the para position.

Alternatively R₁ may be an attachment to a solid phase material, such as polystyrene. Preferably the attachment is of the formula -C(O)-P, -C(O)-OP, -C(O)-NR'-P, -R₁₂-NR'-P, -R₁₂-OP, -NR'-P, -C(O)-R₁₂-P, -C(O)-OR₁₂-P, -C(O)-NR'-R₁₂-P, -R₁₂-NR'-R₁₂-P, -R₁₂-OR₁₂-P, -NR'-R₁₂-P or -R₁₂-P, wherein R', R'' and R₁₂ are as defined above and P is a solid phase material. More preferably R₁ is -C(O)-OP, -C(O)-OR₁₂-P, -C(O)-NH-P, -C(O)-NH-R₁₂-P, -NH-R₁₂-P or -R₁₂-P, wherein R₁₂ is methyl, e.g. -CH₂-P.

R₂ is preferably a reactive substituent suitable for linking the compound to a biological oligomer or polymer, or a monomer unit thereof, e.g. an amino acid or polypeptide. R₂ may suitably be hydroxy, acylamino, acyloxy, amino, halogeno, sulfhydryl, C₁₋₁₀-alkoxy or C₆₋₁₀-aryloxy, preferably halogeno.

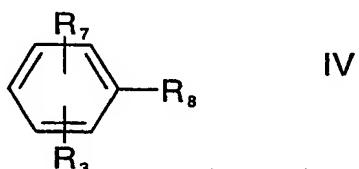
Each benzene ring shown in formulae I to VII may be substituted by one or more groups. For example R₃ may designate one to four substituent groups, preferably one or two substituent groups, attached to the benzene ring shown in formulae I, II and IV to VII. R₄ and R₅ may designate one to five substituent groups, preferably one to three substituent groups, attached to each of the benzene rings shown in formulae I, II and IV to VII. Each substituent group may be present at any suitable position on the benzene rings to which they are attached. More preferably R₄ and/or R₅ is a substituent group at the ortho or para position on the benzene ring to which it is attached.

Each of R₃, R₄ and R₅ may be protected by a removable protecting group if necessary, e.g. when it contains an -OH or -NH₂ group which does not participate in the reaction. Protecting groups, their introduction and removal are described, for example, in "Protective Groups in Organic Synthesis", T. W. Greene et al., John Wiley & Sons Inc., Second Edition 1991. Preferably each of R₃, R₄ or R₅ is a group which does not require protection, e.g. any of the groups listed above other than hydroxy, amino or nitro.

When R_3 , R_4 or R_5 is halogeno, it is preferably fluoro or chloro. When R_3 , R_4 or R_5 is haloalkyl it is preferably trifluoromethyl. Preferably R_3 is C_{1-4} -alkyl, halogeno, or hydrogen. Preferably R_4 and R_5 are each independently C_{1-4} -alkylcarbamoyl, di- C_{1-4} -alkylcarbamoyl, carbamoyl, trifluoromethyl, fluoro or chloro. Preferably R_4 and R_5 are the same.

Preferably the nucleophilic substituents R_6 and R_7 are each independently halogeno, more preferably bromo or iodo, and most preferably R_6 and R_7 are each bromo. R_7 may suitably be in the para, ortho or meta position, preferably in the para position.

In one embodiment of the invention, the compound of formula II is first reacted with the metal or organometallic compound to form a compound of formula IV:



wherein R_3 and R_7 are as defined above and R_8 is $-M$ or $-MX$, where M is metal and X is a nucleophilic substituent, preferably halogeno.

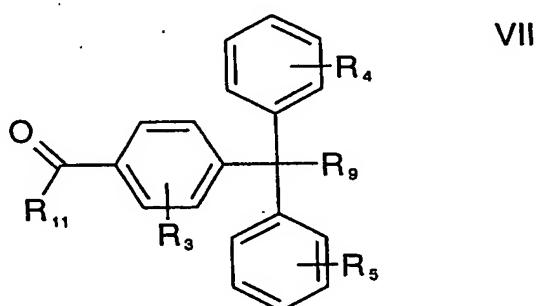
Where the metal is lithium or the organometallic compound is an organolithium compound, R_8 is $-Li$. Where the metal is magnesium or the organometallic compound is a Grignard reagent, R_8 is $-MgX$, and X is preferably halogeno. The compound of formula IV is then reacted with a compound of formula III to form a compound of formula V.

The compounds of formulae IV and V need not be separated or isolated but may be prepared *in situ*.

Suitable electrophiles for use in step (b) include carbon dioxide, isocyanates, nitriles, acyl halides (such as phosgene), leading to the formation of, for example, compounds of formula I wherein R_1 is carboxy, carbamoyl, alkylcarbamoyl or acyl. Alternatively the electrophile may be a derivatised solid phase material, e.g. a Merrifield polymer, enabling direct coupling of the compound of formula VI to a solid phase. In one embodiment the electrophile is a compound of formula $X'-(CH_2)_n-P$, wherein X' is a nucleophilic substituent e.g. halogeno or tosyloxy, n is an integer between 1 and 4, preferably 1, and P is a solid phase material.

Where the electrophile is carbon dioxide, step (b) preferably comprises first reacting the compound of formula V with a metal or organometallic compound to form a compound of formula VI as defined above and reacting, preferably in situ, the compound of formula VI with carbon dioxide.

Where the electrophile is carbon dioxide, preferably a compound of formula VII is formed:



wherein R₃, R₄, R₅ and R₉ are as defined above; and
R₁₁ is -OH, -OM or -OMX, where M is metal and X is a nucleophilic substituent, preferably halogeno, in salt or free form.

Alternatively, the carboxylation step comprises reacting a compound of formula V with carbon dioxide in the presence of a metal or organometallic compound, to form a compound of formula VII.

The hydrolysis step in b) ii) preferably comprises reacting a compound of formula VII wherein R₁₁ is -OM or -OMX and/or R₉ is -OM or -OMX with water or an acid yielding a compound of formula I wherein R₁ is carboxy and R₂ is hydroxy, in salt or free form. Suitable acids include ammonium chloride, acetic acid, sulphuric acid and hydrochloric acid. A pH-buffered solution may also be used. Preferably a weak acid is used and/or the step may be carried out at a pH of 4 to 7. The reaction temperature may conveniently be -50 to 50°C, preferably -10 to 10°C.

Alternatively the compound of formula VII where R₁₁ is -OM or -OMX may be reacted with a nucleophile, e.g. an amine or halide, to form a compound of formula I wherein R₁ is -C(O)-NR'R'' or -C(O)-X and R', R'' and X are as defined above.

Step (a) may conveniently be carried out in an inert organic solvent, preferably an ether solvent, for example diethyl ether or tetrahydrofuran. Alternatively a hydrocarbon solvent may be used. The reaction temperature for step (a) is conveniently -30 to -100°C, preferably -50 to -70°C. The reaction may, for example, be carried out using 0.5 to 2 equivalents, preferably 0.8 to 1.2 equivalents and most preferably about 1 equivalent of the metal or organometallic compound per equivalent of the compound of formula II. 0.5 to 2 equivalents, preferably 0.8 to 1.2 equivalents of the compound of formula III may be used per equivalent of the compound of formula II.

Step (b) may conveniently be carried out in an inert organic solvent as above. The reaction temperature may conveniently be -30 to -100°C, preferably -50 to -70°C. Preferably 0.5 to 2 equivalents, more preferably 0.8 to 1.2 equivalents of a metal or organometallic compound per equivalent of the compound of formula V are used.

The groups R₁ and R₂ may be converted to alternative R₁ and R₂ groups specified above by standard processes, such as by esterification, amidation or nucleophilic substitution. For example, a compound of formula I wherein R₂ is hydroxy may be converted to a compound of formula I wherein R₂ is halogeno by reaction with an acyl halide, e.g. acyl chloride.

Preferably the compound of formula I is in free form. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization.

Compounds of formula I can be recovered from the reaction mixture and purified in a conventional manner.

The starting compounds of formula II or formula III are known or may be prepared by methods analogous to those known in the art. Organometallic compounds may be prepared by standard processes, for example by reaction of an alkyl or aryl halide with a metal, for example lithium or magnesium, suspended in diethyl ether or tetrahydrofuran. The organometallic compound is preferably prepared and used in an inert (oxygen-free) anhydrous atmosphere, for instance under nitrogen.

The process according to the invention may suitably include a further step of coupling the compound of formula I wherein R₁ is a reactive substituent to a solid phase material. Suitable solid phase materials are disclosed, for example, in DE 4306839 A1, and include naturally occurring or synthetic organic or inorganic polymers in particulate form, e.g. as beads, or preferably as a surface layer on a suitable inert substrate material. Examples of suitable polymer materials include crosslinked polystyrene, e.g. polystyrene pins, Gly-HMD-MA/DMA pins and HEMA pins. The compound of formula I may conveniently be coupled to a solid phase material by reacting a group present on the solid phase with R₁. Preferably a compound of formula I, wherein R₁ is a carboxy group or an activated carboxy group, e.g. as disclosed in the example, is reacted with a polymer bearing free amino groups.

The process according to the invention may also suitably include a further step of coupling the compound of formula I, optionally bound to a solid phase material, to a biological oligomer or polymer, or a monomer unit thereof. The compound may conveniently be coupled to the biological molecule, e.g. an amino acid or polypeptide, by reacting a group present on the biological molecule with R₂. For example, where R₂ is hydroxy and the biological molecule is a polypeptide or amino acid, the terminal carboxylic acid group of the biological molecule can be esterified by the R₂ hydroxy group, optionally via initial reaction of the compound of formula I with an acyl halide leading to *in situ* substitution of hydroxy by halogeno.

The invention will now be described with reference to the following specific embodiments.

Example 1

Preparation of 4-(diphenyl-hydroxy-methyl)-benzoic acid

1,4-dibromobenzene (47.2 g, 0.2 M) is added to tetrahydrofuran (THF, 240 ml). The clear solution is cooled to -65°C. A butyllithium solution (0.22 M, 94 ml of a 20% solution in CHX) is added over 30 minutes.

After 5 minutes of stirring a solution of benzophenone (36.4 g, 0.2 M in 180 ml THF) is added over 30 minutes (exothermic). The mixture is stirred for a further 30 minutes at -65°C. Then over 30 minutes the temperature is raised to -10°C and the solution is stirred at this temperature for one hour.

The reaction mixture is then re-cooled to -65°C . Over 30 minutes a butyllithium solution (0.22 M, 94 ml of a 20% solution in cyclohexane) is added.

The resulting suspension is diluted with 200 ml THF. Then carbon dioxide gas is introduced over 90 minutes at -65°C . The temperature is raised to 20°C and the mixture stirred overnight. The mixture is then cooled to 0°C and an aqueous solution of ammonium chloride (120 ml of a 10% solution) is added over 30 minutes. 4-(diphenyl-hydroxy-methyl)-benzoic acid is formed at this stage.

The mixture is evaporated at 45°C under a vacuum. The residue is adjusted to pH 4 with acetic acid and mixed with 400 ml H_2O . Extraction is performed with 2 x 150 ml ethyl acetate. The organic phases are extracted again with 100 ml water. The combined EST-phases are shaken with a 10% aqueous potassium hydroxide solution (2 x 120 ml). The combined aqueous phases are adjusted to pH 1-2 with hydrochloric acid at 20°C and then extracted with 2 x 150 ml TBME-(tert-butyl methyl ether). The combined TBME phases are mixed with 50 ml water and 50 ml saturated Na_2SO_4 , dried with magnesium sulphate and evaporated at 45°C under vacuum to obtain a crude product.

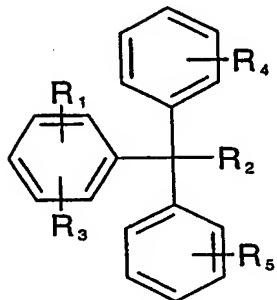
38.3 g crude product is dissolved in TBME (300 ml) at 40°C . The clear yellow solution is concentrated in a volume of 60 ml (240 ml TBME distilled off). The mixture is stirred for one hour at 40°C (crystallisation). 50 ml HPTF is added, the mixture is cooled to 0°C and stirred at 0°C for 1 hour. Evaporating and washing with 2 x 15 ml heptane fraction and drying overnight at 45°C under vacuum gives white crystals.

Attachment of 4-(diphenyl-hydroxy-methyl)-benzoic acid to a solid phase

15g 4-(diphenyl-hydroxy-methyl)-benzoic acid with 7.54 g hydroxybenzotriazole is dissolved in 140 ml dimethylformamide (DMF) by stirring for 15 min. 15.3 ml di-isopropylcarbo-di-imide is added and the solution kept at room temperature for 30 min. The solution is then stirred overnight at room temperature in the presence of aminomethylated polystyrene. After washing with DMF, methanol and THF the linker derivatised support is dried under vacuum.

Claims

1. A process for preparing a compound of formula I or a salt thereof

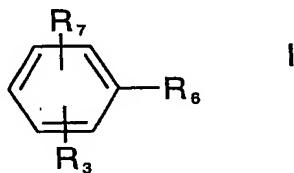


wherein R₁ is a reactive substituent or an attachment to a solid phase;

R₂ is a reactive substituent; and

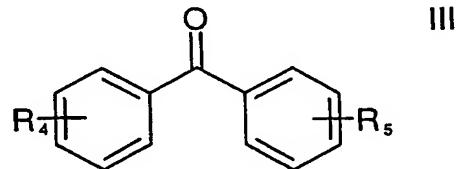
R₃, R₄ and R₅ are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, C₁₋₁₀-alkylamino, di-C₁₋₁₀-alkylamino, carbamoyl, C₁₋₁₀-alkylcarbamoyl, di-C₁₋₁₀-alkylcarbamoyl, halo-C₁₋₁₀-alkyl, halogeno or nitro; comprising

- (a) (i) reacting a compound of formula II with a metal or organometallic compound



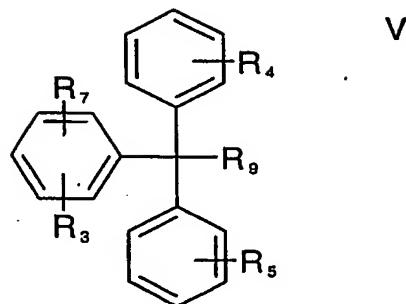
wherein R₆ and R₇ are each a nucleophilic substituent and R₃ is as defined above and is protected if necessary by a removable protecting group; and

- (ii) reacting the compound obtained in (i) with a compound of formula III



wherein R₄ and R₅ are as defined above and are protected if necessary by a removable protecting group;

to form a compound of formula V

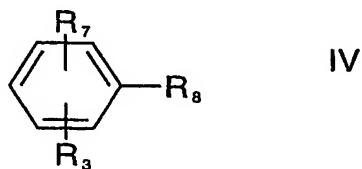


wherein R_3 , R_4 , R_5 and R_7 are as defined above;

R_9 is $-OH$, $-OM$ or $-OMX$, where M is metal and X is a nucleophilic substituent; and

- (b) (i) reacting the compound of formula V with a metal or organometallic compound, and
 - (ii) reacting the compound obtained in (b) (i) with an electrophile, and hydrolysing the resulting compound to form a compound of formula I wherein R_2 is hydroxy;
- (c) optionally converting the hydroxy as R_2 to an alternative R_2 group;
- (d) optionally converting R_1 to an alternative R_1 group;
- (e) optionally deprotecting a compound of formula I in protected form; and
- (e) where required, converting a compound of formula I obtained in free form into the desired salt form, or vice versa.

2. A process according to claim 1, wherein step (a) (i) comprises forming a compound of formula IV



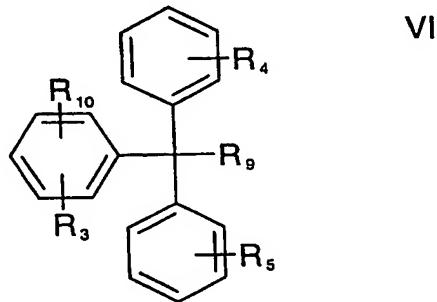
wherein R_3 and R_7 are as defined above and R_8 is $-M$ or $-MX$, where M is metal and X is a nucleophilic substituent;

and step (a)(ii) comprises reacting the compound of formula IV with the compound of formula III.

3. A process according to claim 1 or claim 2, wherein the organometallic compound comprises an alkylolithium compound.

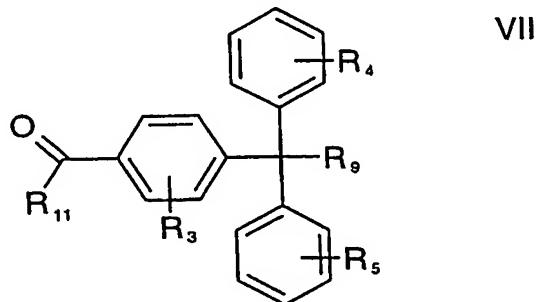
4. A process according to claim 3, wherein the alkylolithium compound comprises butyllithium.

5. A process according to any preceding claim, wherein R₁ is carboxy.
6. A process according to any preceding claim, wherein R₂ is hydroxy.
7. A process according to any preceding claim, wherein R₆ and R₇ are each independently bromo or iodo.
8. A process according to any preceding claim, wherein step (b) comprises
(i) reacting the compound of formula V with a metal or organometallic compound to form a compound of formula VI, in free or salt form:



wherein R₃, R₄, R₅ and R₉ are as defined above; and
R₁₀ is -M or -MX, where M is metal and X is a nucleophilic substituent;
and reacting the compound of formula VI with carbon dioxide.

9. A process according to claim 8, wherein step (b) comprises forming a compound of formula VII:

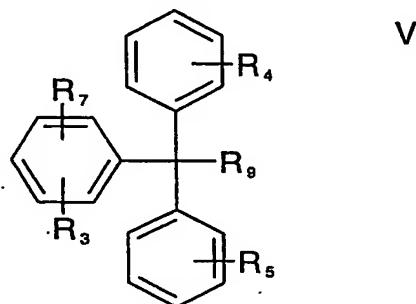


wherein R₃, R₄, R₅ and R₉ are as defined above; and

R₁₁ is -OH, -OM or -OMX, where M is metal and X is a nucleophilic substituent, in salt or free form.

10. A process for the preparation of a solid phase support system, comprising preparing a compound of formula I by a process as defined in any of claims 1 to 9, and coupling the compound with a suitably derivatised or functionalised solid phase material.

11. A compound of formula V in free or salt form



wherein R₃, R₄ and R₅ are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, C₁₋₁₀-alkylamino, di-C₁₋₁₀-alkylamino, carbamoyl, C₁₋₁₀-alkylcarbamoyl, di-C₁₋₁₀-alkylcarbamoyl, halo-C₁₋₁₀-alkyl, halogeno or nitro, optionally protected by a removable protecting group;

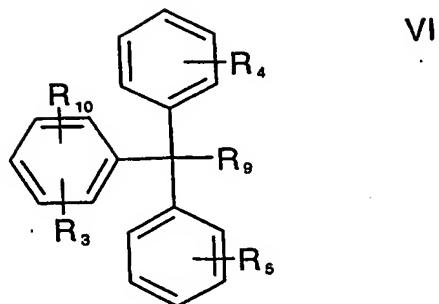
R₇ is a nucleophilic substituent; and

R₉ is -OH, -OM or -OMX, where M is metal and X is a nucleophilic substituent.

12. A compound according to claim 11, wherein R₇ is bromo or iodo.

13. A compound according to claim 11 or claim 12, wherein R₉ is -OLi, -OMgBr, -OMgI or -OH.

14. A compound of formula VI in free or salt form



VI

wherein R₃, R₄ and R₅ are each independently hydrogen or one or more substituents attached to each benzene ring, and are selected from hydroxy, amino, C₁₋₁₀-alkyl, C₁₋₁₀-alkoxy, C₁₋₁₀-alkylamino, di-C₁₋₁₀-alkylamino, carbamoyl, C₁₋₁₀-alkylcarbamoyl, di-C₁₋₁₀-alkylcarbamoyl, halo-C₁₋₁₀-alkyl, halogeno or nitro, optionally protected by a removable protecting group; R₉ is -OH, -OM or -OMX, where M is metal and X is a nucleophilic substituent; and R₁₀ is -M or -MX, where M is metal and X is a nucleophilic substituent.

15. A process substantially as hereinbefore described with reference to the example.

16. A compound of formula V or formula VI substantially as hereinbefore described with reference to the example.